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I, LEANNE MYNOTT, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ 1325 for a patent by COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION filed on 01 July 1999.

WITNESS my hand this
Fourteenth day of July 2000

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ORIGINAL

PROVISIONAL SPECIFICATION FOR AN INVENTION ENTITLED

Invention Title: NASOGASTRIC ENTERAL FORMULATIONS

Name of Applicant: COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION

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The invention is described in the following statement :

This invention relates to an enteral formulation suitable for nasogastric administration.

BACKGROUND OF THE INVENTION

Humans and animals with certain conditions are either not able to or preferably do not take nutrition by conventional mean. Such individuals can have sustenance administered parenterally such as by the use of a venous drip or enterally in the form of a specific formulation delivered via the gastrointestinal tract. There are obvious disadvantages in administering sustenance parenterally in so far as the risk of infection is greatly increased and the rate at which material that can be administered is quite low. Moreover, certain types of material cannot be administered, for example, dietary plant fibre. Additionally there are dangers in having a gastrointestinal system which is inactive for any extended length of time as it can lead to atrophy and to a range of other histo-pathological changes to various regions.

Food formulations for clinical conditions may be administered orally and that is the preferred route as it is the normal means of food ingestion. However, for certain specific conditions it is necessary or at least advantageous to administer the formulation enetrally by means of a nasogastric tube which delivers nutrients to the stomach.

Enteral feeding goes some way to alleviating the problems of a totally inactive gastrointestinal tract. However, under most circumstances most of the nutrients of the so called elemental diets that are administered in this way are adsorbed before reaching the large bowel. As a consequence can lead to disorders of the caecum and colon due to their inactivity. Such disorders might include atrophy and perforation of the bowel, and the overgrowth of the normal microflora of the bowel by organisms which might potentially be pathogens.

Even where normal ingestion of food takes place it appears that many of the disorders of the large bowel can be attributable to its inactivity and also to the inactivity of bacteria which inhabit it. It has been found that products of bacterial fermentation of carbohydrates and other dietary components (such as proteins), namely short chain fatty acids (SCFAs), have direct beneficial effects in the bowel if administered as enemas and may constitute a means to ameliorate at least some of the disorders. However where they are ingested orally, SCFAs are metabolised before reaching the large bowel so that they have little therapeutic benefit. SCFA levels in the large bowel can only be increased via oral intake by an increased consumption of carbohydrates that are resistant to digestion in the small intestine and which therefore are able to reach the caecum and colon in adequate quantities to be acted on by the local microflora to produce SCFAs.

Additional benefits to large bowel health may be gained by the ingestion of carbohydrates not digested in the small intestine in that they assist with increasing bulk, enhance water retention and support the growth of non-pathogenic micro-organisms in the large bowel. Without these further effects, the greater availability of SCFAs will only partially address the deficiencies causing large bowel disorders.

The difficulty of large bowel disorders resulting from enteral feeding regimes has been recognised and a number of suggestions have been made to alleviate it.

For example, Cope *et al* in US patent 5403826 suggest the inclusion of dietary fibre to enteral formulations and specifically trial the use of soy polysaccharides. These polysaccharides are digested in the ileocecal region and in the large bowel resulting in the production of short chain fatty acids which is said by the authors to add bulk to stools and help to increase water retention to minimise HIV inflicted diarrhoea.

It is known that polysaccharides resistant to small intestinal digestion are fermented principally in the proximal large bowel and that relatively little goes as far as the distal colon (Annison, G. & Topping, D.L. (1994) Resistant starch: Chemical structure vs physiological function. Ann. Rev. Nutr. 14: 297-320). The distal large bowel is often particularly adversely affected by atrophy and perforation and it is the view of the present inventors that the Cope teaching does not alleviate disorders for the distal large bowel. Cope does not teach the delivery of sufficient bulking fibre to sustain large bowel micro flora, and particularly for the distal large bowel. The addition of soy polysaccharide at the levels provided by Cope *et al* (about 1%) is not sufficient to provide SCFA at quantities in the large bowel sufficient to give a measurable health benefit for the large colon. Moreover, the addition of soy polysaccharide at the level suggested by Cope *et al* will have a negligible impact on supporting the microflora in the large bowel, and thus will not add appreciably to the bulk of microflora mass in the large intestine, and/or the water retention therein.

Garleb *et al* in US patent 5444054 also discuss the prospect of delivering digestible material to the large bowel in the form of dietary fibres and indigestible oligosaccharides so that SCFAs may be formed.

The problems with the Cope and Garleb suggestions are that they have not addressed the matter of the addition of sufficient bulk and nutrient that can be delivered to the large bowel to support a sufficient population of microflora therein as well as to support the production of an adequate supply of SCFA via nasogastric administration to alleviate

the bowel dysfunction that otherwise results from feeding using enteral formulations. The problem addressed by these two workers has been explored using orally ingested enteric formulations.

Enteral feeds are intended to replace the normal diet and so contain materials that reflect such diets, and these include nitrogenous material such as proteins, peptides or amino acids, carbohydrates (whole or partially hydrolysed), lipids, vitamins and essential minerals are thus generally delivered as emulsions. In addition some of the components may also be delivered as insoluble suspensions. However, the provision of insoluble suspensions is particularly undesirable for nasogastric application, because of the difficulties associated with sedimentation and phase separation and the difficulty of resorting to increased viscosities to alleviate settling out. The very much preferred approach to nasogastric application is to provide the solids in soluble form, which are supplied together with the fat component form an emulsion.

A major restriction in naso gastric administered formulations is in terms of the quantity of material that can be administered and the capacity of the tube to allow the flow of material. Nasogastric tubes are rather difficult to put into place and are unpleasant for the patient and thus the outside diameter of the tube is kept as small as possible with a consequent small internal diameter. Not only is the internal diameter a consideration but a pump is generally used to push the formulation through the tube. This means that the liquid within the tube is also under compression, so that any viscosity of the fluid is further compounded. The intrinsic viscosity of soluble fibre and protein in the partially or fully hydrolysed state can be high and poses a limitation.

OBJECT OF THE INVENTION

It is an object of the present invention to provide an enteral formulation for nasogastric application which reduces the disadvantages to large bowel health.

SUMMARY OF THE INVENTION

WO 95/13801 in the name of the Commonwealth Scientific and Industrial Research Organisation discloses a means of enhancing the levels of short chain fatty acids delivered to the bowel to alleviate or overcome some disorders of the large bowel.

The present inventors now recognise that there are prospects of developing a workable enteral formulation suitable for nasogastric application which can reduce the problems associated with a physiologically inactive large bowel.

It is proposed by this invention to provide for an enteral formulation suitable for use in nasogastric feeding, which includes a fatty acid delivery agent for enhanced delivery of fatty acids to the large bowel that have a beneficial effect in the large bowel. The fatty acids in the fatty acid delivery agent are covalently bonded to a carrier by a bond that is selectively cleavable in the large bowel to give free fatty acids. The fatty acid delivery agent is either soluble in water or the lipid phase of the prepared formulation or alternatively can be rendered stable by an emulsifying agent such as by packaging into liposomes. Most preferably the fatty acid delivery agent is soluble.

The fatty acids are selected as being of benefit to the health of the individual human or animal. The fatty acid might be one or more of the short chain fatty acids, which in the present context might be taken as having a carbon chain length of between 1 and 10. More preferably however the chain length is between 2 and 4, encompassing acetate, propionate and butyrate, from the literature these three SCFAs have the most evident health benefits. Alternatively a broader range of fatty acids might also be contemplated by this invention, which fatty acids play a role in benefits other than bowel health directly, and such fatty acids might be selected from the omega 3 fats (such as eicosapentaenoic acid, EPA) and docosahexenoic acid DHA), omega 6 fats (such as linoleic acid), and conjugated fatty acids (such as conjugated linoleic acid). These fats may be given as triacylglycerols or partial glycerides or as phospholipids bonded to the carrier. The formulation might also include drugs such as amino salicylic acid (5ASA) to alleviate colitis or other conditions.

The carrier can be varied greatly and might include natural fibre or resistant oligosaccharides or other biological molecules, alternatively a synthetic polymer might be used as the carrier. The carrier might thus be contemplated as being a faecal bulking agent. The invention however contemplates that the carrier will be capable of being used as an energy source for normal large bowel microflora. Generally it is anticipated that the carrier will preferably be a carbohydrate so that on cleavage of the fatty acid from the carrier, the carrier can then be used, firstly as a means for increasing the microflora of the large bowel, and secondly can be metabolised by at least a proportion of the microflora to form SCFA, to further enhance health benefits to the large colon. More preferably the carrier is a starch and most preferably a resistant starch.

The degree of substitution is also of relevance in so far as many carriers that might be contemplated such as for example hydrolysed carbohydrates would have a tendency to exert osmolarity effects that might, for example, give rise to diarrhoea. The latter condition is predisposed to some extent already by the adoption of a radically different diet and the absence of SCFA which facilitates fluid absorption. Whereas with suitable

substitution the nature of a carrier molecule can be modified, so as to be a little more conducive to water retention by the large bowel. Additionally where the carrier is a natural carbohydrate such as a starch the substitution has a tendency to minimise gelatinisation, especially under heat treatment, thereby maintaining the resistance of the formulation after treatment for sterilisation. Additionally this will impact positively on the viscosity of the prepared formulation.

Examples of the bond between the fatty acid and the carrier are amide or ester bonds.

Other examples of fatty acid delivery agents can be determined by reference to WO 95/13801 which document is hereby incorporated by reference.

In one aspect of the present invention it is proposed that the nasogastric elemental diet formulation include a

a) an amino acid source
b) a sugar source
c) a lipid source
d) a mineral source
e) a vitamin source
f) and a fatty acid delivery agent as discussed and described herein.

It might also be desired to add further components for example anti-oxidants and additional pharmaceutical therapeutics.

The sources of a) to e) are generally conventional sources selected from those that do not interfere with nasogastric application, and do not adversely react with f). The sugar source may take the form of carbohydrates, which in part form the carrier of the fatty acid delivery agent where the carrier is a carbohydrate. Preferably however these are added separately so that metabolism and absorption can be achieved in the small bowel. The level of f) is sufficient to deliver a beneficial quantity of the combination of a bulking agent and Fatty Acid to the large bowel, and preferably the level of f) is in the range of greater than 5 grams per day, with the maximum being limited by viscosity constraints, and might be less than 30 grams per day. More preferably f) is in the range of 1- to 20 grams per day and in the case of a SCFA substituted resistant starch substituted at a degree of substitution of 0.2 the level is most preferably about 18 grams per day.

It is anticipated that the fatty acid delivery agent is made by taking a carrier and substituting fatty acids onto the carrier.

The daily dosage rate for a fatty acid delivery which takes the form of a resistant maize starch substituted by 2 - 4 carbon length SCFA at a degree of substitution of 0.1 could be in the range of 5 to 20 grams per day. This might be compared to a similar level of resistant starch requiring to be delivered at a rate in excess of 25 grams per day, to give the amount of SCFA required and demonstrated in W095/13801, and by Sheppach et al. (1992) *Gastroenterology*; 10: 51-56). Given that the level of fluid delivery of enteral feeds is in the vicinity of 1 litre, the level of conventional carbohydrate required to be present (about 2.5% w/v), in addition to other constituents (such as those known to the skilled addressee) of the enteral feed is in vast excess of what would not, by reason of viscosity, be readily deliverable through a nasogastric tube. Beneficial effects of the fatty acid delivery agent may however be of value at a greater range of levels, and perhaps as low as 0.5% w/v of the final enteric formulation, the upper limit might be determined by solubility and thus might perhaps account for as much as 5% of the final enteric formulation as administered through the nasogastric tube.

Additionally the benefit of the present formulation is that the level of a predetermined Fatty Acid can be increased in the large bowel. Thus, for example, a butyrated starch could be added to specifically increase the level of butyrate in the large bowel.

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